1043 INTRATUMORAL MRNA IL-12 CAN INDUCE A DOSE DEPENDENT IMMUNOSTIMULATORY EFFECT WITHIN TUMOR MICROENVIRONMENT IN PATIENTS WITH ADVANCED SOLID TUMORS

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Background MEDI1191 is an investigational therapy composed of mRNA encoding interleukin-12 (IL-12p70) in a lipid nanoparticle optimized for intratumoral injection. Previously[1] [2] we reported that all dose levels induce pharmacodynamic (PD) changes such as elevated serum IL-12, increased T cell infiltration and upregulation of immune gene signatures associated with anti-tumor responses. Since the actual dose and drug distribution may be affected by injected lesion size, we hypothesize that a normalized dose (ND) to lesion size will accurately reflect the dose effect and PD changes within tumor microenvironment (TME).

Methods In a phase 1 dose escalation study (NCT03946800), patients received 0.1–12 μg MEDI1191 sequentially (Part 1A) or concurrently (Part 1B and Part 1D) with intravenous durvalumab (1500 mg). To determine the dose effect on PD changes within the TME, we calculated a normalized dose (μg/mm) for each patient by dividing the first actual injected dose by the longest (for non-lymph node lesions) or shortest (for lymph node lesions) diameter of injected lesions (14–130 mm).

Results The first administration induced serum IL-12 levels at all dose levels and the total IL-12 exposure measured by area under the curve was induced in a dose-dependent manner. Patients dosed at 8 and 12 μg had higher normalized dose (0.08–0.75 μg/mm) than patients dosed at 0.1–3 μg (0.002–0.15 μg/mm). High normalized dose (ND^{hi}) elevated serum IL-12 and IFN-γ levels at 24h following injection to a greater extent than low normalized dose (ND^{lo}).

To correlate the dose effect with PD changes within the TME, we looked at the immune gene signatures in 14 patients (7 patients in each dose group) with available paired biopsies at screening and day 15. The gene set enrichment analysis revealed an increased enrichment of the hallmark interferon-gamma response pathway in ND^{hi}patients. The average scores of gene signatures such as T cell inflamed, cytotoxic activity and T cell proliferation were induced in ND^{hi}patients, whereas ND^{lo}patients showed decrease or no major changes. Lesions of ND^{hi}patients exhibited an inflammatory phenotype post-treatment. The best anti-tumor PD effect was observed in a partial responder in the ND^{hi} group, which was associated with the largest increase in tumoral CD8 T cell density (6-fold) and PD-L1 (8.5-fold) by immunohistochemistry at injected lesions.

Conclusions Intratumoral injection of mRNA IL-12 can induce an immunostimulatory effect, including elevated anti-tumor gene signatures and T cell infiltration. Evidence of a dose-dependent immune modulation within the TME was observed at injected lesion sites.

Trial Registration NCT03946800

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Ethics Approval The IRB/IEC responsible for each site reviewed and approved the final study protocol, including the final version of the ICF and any other written information and/or materials to be provided to the subjects. Institutional Review Boards, Mount Sinai Health System, New York (Board Number 19–00279).

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